84. (New) The method of Claim 42 comprising administering to the mammal a soluble polypeptide comprising the extracellular domain of an Ephrin family ligand or a soluble polypeptide comprising the extracellular domain of an Eph family receptor, thereby inhibiting the growth of blood vessels.

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85. (New) The method of Claim 42 comprising administering to the mammal a soluble polypeptide comprising the extracellular domain of an Ephrin family ligand or a soluble polypeptide comprising the extracellular domain of an Eph family receptor, thereby enhancing the growth of blood vessels.

REMARKS

Claims 1, 2, 8, 9, 22-41 and 44-71 have been cancelled, Claims 3-7, 10-12, 42, 43, 72 and 75 have been amended, and Claims 76-85 have been added. No new matter has been added. Claims 3-7, 10-13, 15-21, 42, 43 and 72-85 are pending.

Amendments to the Specification

At page 7, line 30, "ligands" has been deleted and "ligand" has been inserted therefor.

At page 12, line 4, "of" has been inserted between "all" and "its".

At page 16, line 31, "the" has been deleted.

At page 21, lines 10 and 13, "veinous" has been deleted and "venous" has been inserted therefor. At line 15, "betweeen" has been deleted and "between" has been inserted therefor. At line 22, "cells" has been deleted and "cell" has been inserted therefor. At line 23, a "," has been inserted after "molecule" and at line 24, a "," has been inserted after "type".

At page 28, lines 2 and 6, "Eph4" has been deleted and "EphB4" has been inserted therefor. Support for the recitation of "EphB4" is found throughout the specification, for example, at page 6, lines 20-21.

At page 38, line 3, "was" has been deleted. At line 6, a "," has been inserted after "vessels" and after "staining". At line 7, a "," has been inserted after "sac".

At page 39, line 17 and page 41, line 9, "â-" has been deleted and "β-" has been inserted therefor. Support for the recitation of "β-galactosidase" is found throughout the specification, for example, at page 37, lines 28-31.

At page 41, line 5, a "," has been inserted after "embryos". At line 14, "Henkemeyer, *et al.*, *Oncogene 9*:1001-1014 (1994)" has been placed in parentheses.

Claims

In the Office Action dated March 8, 2000 (Paper 9, Page 3), the Examiner stated:

> Applicant is required under U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently claims 1-3, 7-10, 12, 15-17, 19, and 41-43 are generic since they do not distinguish between agonists and antagonists. Claims 1-7 and 41-43 are also generic because they do not distinguish between artery-specific and vein-specific molecules.

The Examiner further stated in this Office Action that:

> Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species.

Thus, Claims 1, 2, 8, 9, 22-41 and 44-71 have been cancelled, Claims 3-7, 10-12, 42, 43, 72 and 75 have been amended, and Claims 76-85 have been added. Claims 3-7, 10-13, 15-21, 42, 43 and 72-85 are pending.

The current generic pending claims are Claims 3-7, 10, 12, 15-17, 19, 41-43, 72-74, 76-78, 80, 84 and 85. Claims readable on the elected species are Claims 3, 5, 7, 10, 12, 42, 43, 72-77, 79, 81-83 and 85. Claims 10-13, 42, 43, 72, 75, 78-80 and 82-85 (as amended) are either written in dependent form or otherwise include all of the limitations of an allowed generic claim (see below, Paragraph 8. Objection to Claims 10, 12, 42 and 43).

Amendments to the Claims

Claims 1, 2, 8, 9, 22-41 and 44-71 have been cancelled, Claims 3-7, 10-12, 42, 43, 72 and 75 have been amended, and Claims 76-85 have been added. Claims 3-7, 10-13, 15-21, 42, 43 and 72-85 are pending.

Claim 3 has been amended and redrafted as an independent claim and includes the subject matter of base Claim 1.

Claim 4 has been amended to delete "or interaction", "artery-specific" and "vein-specific" and to recite "the specific binding". Support for the recitation of "specific binding" can be found throughout the specification, for example, at page 28, lines 1-24.

Claim 5 has been amended to delete "interaction", "artery-specific" and "its vein-specific" and to recite "specific binding". Support for the recitation of "specific binding" can be found throughout the specification, for example, at page 28, lines 1-24.

Claims 6 and 7 have been amended to delete "artery-specific" and "vein-specific".

Claim 10 has been amended and redrafted as an independent claim and includes the subject matter of base Claim 8.

Claims 11 and 12 have been amended to delete "artery-specific".

Claim 42 has been amended and redrafted as an independent claim and includes the subject matter of base Claim 41.

Claim 43 has been amended to delete "and the Eph family receptor is EphB4" and to recite "comprising administering to the mammal a soluble polypeptide comprising the extracellular domain of an Ephrin family ligand." Support for the recitation can be found, for example, at page 28, lines 19-24 and in Claims 42 and 43 as originally filed.

Claim 72 has been amended to depend from Claim 10.

Claim 75 has been amended to depend from Claim 12.

Support for new Claims 76-81 is found throughout the specification, for example, at page 30, lines 3-30.

Support for new Claims 82 and 83 is found throughout the specification, for example, at page 28, line 28-31.

Support for new Claims 84 and 85 is found throughout the specification, for example, at page 29, line 25 to page 30, line 2.

The amendments to the specification and claims are supported by the parent application as originally filed. Therefore, this Amendment adds no new matter.

Additional remarks addressing the rejections set forth in the Office Action are set forth below with reference to the numbered paragraphs in the Office Action.

Paragraph 5. Rejection of Claims 1, 2, 8, 9 and 41 Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 8, 9 and 41 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement commensurate with the scope of the claims. Claims 1, 2, 8, 9 and 41 have been cancelled thereby obviating the rejection of these claims on this basis.

Paragraph 6. Rejection of Claims 1, 2, 8, 9 and 41 Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 8, 9 and 41 are rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Claims 1, 2, 8, 9 and 41 have been cancelled thereby obviating the rejection of these claims on this basis.

Paragraph 7. Rejection of Claims 1-3, 5 and 7 Under 35 U.S.C. § 112, second paragraph

Claims 1-3, 5 and 7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 1 and 2 have been cancelled thereby obviating the rejection of these claims on this basis. Claims 3, 5 and 7 have been amended to recite "specific binding" which the Examiner has indicated will overcome this rejection (Office Action dated October 24, 2000 (Paper Number 14), page 4, paragraph 6).

Paragraph 8. Objection to Claims 10, 12, 42 and 43

Claims 10, 12, 42 and 43 are objected to as depending from base claims which the Examiner has not deemed allowable. Claims 10 and 42 have been amended and redrafted as independent claims which include all of the subject matter of their respective base claims. As such, and as indicated by the Examiner (Office Action dated May 17, 2001 (Paper Number 18), page 4, paragraph 8) these claims are now allowable. Claims 12 and 43 are allowable because they depend from independent Claims 10 and 42 respectively, which the Examiner has indicated would be allowable as amended.

Paragraph 9. Objection to Claims 3, 7, 10 and 12 Under 37 C.F.R. § 1.75

The Examiner has stated that should Claims 67, 68, 69 and 71 be found allowable, Claims 3, 7, 10 and 12 will be objected to under 37 C.F.R. § 1.75, as being substantial duplicates thereof. Claims 67, 68, 69 and 71 have been cancelled thereby obviating the objection of Claims 3, 7, 10 and 12 on this basis.

Paragraph 10. Provisional Rejection of Claims 1-3, 5, 7-10, 12, 41-44, 67-69, 71 and 72 Under 35 U.S.C. § 101

Claims 1-3, 5, 7-10, 12, 41-44, 67-69, 71 and 72 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of Claims 1-3, 5, 7-10, 12, 42-44, 3, 7, 10, 12 and 14 respectively, of co-pending Application No. 09/687,652. Claims 1, 2, 8, 9, 67-69 and 71 have been cancelled thereby obviating the provisional rejection of these claims on this basis.

As noted by the Examiner, the rejection is a provisional rejection because the claims of co-pending U.S. Patent Application No. 09/687,652 have not been patented. Applicants will address the rejection of remaining Claims 3, 5, 7, 10, 12, 41-44, 71 and 72 in the subject application if the claims of co-pending U.S. Patent Application No. 09/687,652 are allowed or patented before the claims of the subject application.

If this provisional rejection is the only rejection remaining after entry and consideration of this Amendment, Applicants request that the Examiner withdraw the rejection and permit the

subject application to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B)).

Paragraph 11. Provisional Rejection of Claims 70 and 73-75 Under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 70 and 73-75 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 14, 71, 72 and 8 respectively, of co-pending Application No. 09/687,652. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope.

Claim 70 has been cancelled, thereby obviating the provisional rejection on this basis. With respect to remaining Claims 73-75, Applicants will consider filing a terminal disclaimer if the claims deemed to be conflicting with those of U.S. Application No. 09/687,652 are indicated as being allowable in the subject application.

Interview Summary

Applicants thank Examiner Andres for the telephonic interview granted January 22, 2001 and further note the attachment of an Interview Summary (PTO Form-413) to the Office Action dated May 17, 2001. In preparing the response Applicants observed that the Examiner did not check box (i) on PTO Form-413. This box states that "it is not necessary for applicant to provide a separate record of the substance of the interview (if box is checked)."

At the end of the telephonic interview on January 22, 2001, Applicants and the Examiner agreed that the Examiner would provide the Interview Summary. Therefore, it is Applicants' belief that box (i) on the PTO Form-413 should have been checked by the Examiner. Accordingly, on July 22, 2001, Applicants' Attorney contacted the Examiner by telephone to confirm that this understanding was correct. In this telephone conversation, the Examiner agreed that box (i) should have been checked as it is a complete summary of the interview. The Examiner then sent by facsimile a duplicate of PTO Form-413 with box (i) duly checked by the Examiner to reflect the understanding of the parties. To clarify the record, Applicants are

attaching hereto a copy of the original Interview Summary (PTO Form-413) provided with the Office Action dated May 17, 2001, as well as a copy of the subsequent Interview Summary (PTO Form-413) sent by facsimile showing the box checked. Accordingly, there is no response nor extension fees due in relation to the interview held on January 22, 2001.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978)341-0036

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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Concord, Massachusetts 01742-9133
Dated: 10/3/01

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 7, line 25 through page 8, line 8 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As described in the examples, a gene which encodes a cell membrane-associated ligand which is present in the nervous system and the vascular system has been shown to be expressed by arterial endothelial cells and not by venous endothelial cells. Further, the gene which encodes the receptor for the [ligands] ligand has been shown to be expressed by venous endothelial cells, but not by arterial endothelial cells. Thus, for the first time, an arterial endothelial cell-(artery-)specific marker and a venous endothelial cell-(vein-)specific marker are available, making it possible to distinguish between arteries and veins for a variety of purposes, such as further study and understanding of the mechanisms of blood vessel formation; selective targeting of treatments or therapies to arteries or veins (targeting to arteries but not veins or vice versa) and selective modulation (enhancement or inhibition) of formation, growth and survival of arteries and/or veins.

Replace the paragraph at page 12, lines 3 through 10 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As used herein, a transgenic mouse is one which has, incorporated into the genome of some or all of its nucleated cells, a genetic alteration which has been introduced into the mouse or at least one of its ancestors, by the manipulations of man. A transgenic mouse can result, for example, from the introduction of DNA into a fertilized mouse ovum or from the introduction of DNA into embryonic stem cells.

Replace the paragraph at page 16, line 19 through page 17, line 10 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

As a result of the work described herein, it is possible to differentiate between arterial endothelial cells (arteries) and venous endothelial cells (veins) by taking advantage of the presence of an artery-specific or vein-specific gene product on the surface of the cells. Arterial endothelial cells and venous endothelial cells can each be isolated from cells of other tissue types by, for instance, excision of artery or vein tissue from a sample of mammalian tissue, dissociation of the cells, allowing the cells to bind, under appropriate conditions, to a substance which has some property or characteristic (e.g., a molecule which provides a label or tag, or molecule that has affinity for both [the] an artery-specific cell surface protein and another type of molecule) that facilitates separation of cells bound to the substance from cells not bound to the substance. Separation of the cells can take advantage of the properties of the bound substance. For example, the substance can be an antibody (antiserum, polyclonal or monoclonal) which has been raised against the protein specific to arterial endothelial cells (or to a sufficiently antigenic portion of the protein) and labeled with a fluorochrome, with biotin, or with another label. Separation of cells bound to the substance can be by FACS, for a fluorescent label, by streptavidin affinity column, for a biotin label, by other affinity-based separation methods, or, for example, by antibody-conjugated magnetic beads or solid supports.

Replace the paragraph at page 21, lines 7 through 31 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A drug that inhibits interaction of an artery-specific cell surface molecule (e.g., an arterial endothelial cell-specific surface molecule) with a vein-specific cell surface molecule (e.g., a [veinous] <u>venous</u> endothelial cell-specific surface molecule) can be identified by a method in which, for example, the arterial endothelial cell-specific surface molecule and the [veinous] <u>venous</u>

endothelial cell-specific surface molecule are combined with a drug to be assessed for its ability to inhibit interaction between the cell-specific molecules, under conditions appropriate for interaction [betweeen] between the cell-specific molecules. The cell-specific molecules may be used in the assay such that both are found on intact cells in suspension (e.g., isolated arterial or venous endothelial cells, immortalized cells derived from these, or cells which have been modified to express an artery- or vein-specific [cells] cell surface molecule); one cell type is fixed to a solid support, and the other molecule, specific to the other cell type, is in soluble form in a suitable solution; or the molecule specific to one cell type is fixed to a solid support while the molecule specific to the other cell type is found free in a solution that allows for interaction of the cell-specific molecules. Other variations are possible to allow for the convenient assessment of the interaction between the two different cell-specific molecules.

Replace the paragraph at page 28, lines 1 through 24 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The differential expression of EphrinB2 in arteries and of [Eph4] EphB4 in veins allows for the specific targeting of drugs, diagnostic agents or other substances to the cells of arteries or of veins. A targeting vehicle can be used for the delivery of such a substance. Targeting vehicles which bind specifically to EphrinB2 or to [Eph4] EphB4 can be linked to a substance to be delivered to the cells of arteries or veins, respectively. The linkage can be via one or more covalent bonds, or by high affinity non-covalent bonds. A targeting vehicle can be an antibody, for instance, or other compound which binds either to EphrinB2 or to EphB4 with high specificity. Another example is an aqueously soluble polypeptide having the amino acid sequence of the extracellular domain of EphB4, or a sufficient portion of the extracellular domain (or a polypeptide having an amino acid sequence conferring a similar enough conformation to allow specific binding to EphrinB2), which can be used as a targeting vehicle for delivery of substances to EphrinB2 in arteries. Similarly, a soluble polypeptide having the amino acid sequence of the extracellular domain of EphrinB2 or a sufficient antigenic portion of the extracellular domain (or a polypeptide having an amino acid sequence

conferring a similar enough conformation to allow specific binding to EphB4), can be used to target substances to EphB4 in veins.

Replace the paragraph at page 38, lines 3 through 11 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Defects in yolk sac angiogenesis [was] were apparent by E9.0 and obvious at E9.5. There was an apparent block to remodeling at the capillary plexus stage, for both arterial vessels, as revealed by β-galactosidase staining, and venous vessels in the anterior region of the sac, as revealed by PECAM staining. Thus, disruption of the EphrinB2 ligand gene caused both a non-autonomous defect in EphB4 receptor-expressing venous cells, and an autonomous defect in the arteries themselves.

Replace the paragraph at page 39, lines 15 through 30 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Similar to the yolk sac phenotype, the capillary bed of the head appeared dilated in the mutant, and apparently arrested at the primary plexus stage. Staining for [â] β-galactosidase revealed that the anterior-most branches of the internal carotid artery failed to develop in the mutant. Unlike the case in the yolk sac, therefore, the malformed capillary beds must be entirely of venous origin. However the anterior branches of the anterior cardinal vein formed although they were slightly dilated. Taken together, these data indicate that in the head, venous angiogenesis is blocked if the normal interaction with arterial capillaries is prevented. The angiogenic defects observed in the head and yolk sac are unlikely to be secondary consequences of heart defects (see below), since they are observed starting at E9.0 and the embryonic blood circulation appears normal until E9.5.

Replace the paragraph at page 41, lines 5 through 19 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In EphrinB2^{tlacZ}/EphrinB2^{tlacZ} embryos, capillary ingrowth into the neural tube failed to occur. Instead, EphrinB2-expressing endothelial cells remained associated with the exterior surface of the developing spinal cord. Comparison of [â] β-galactosidase to pan-endothelial PECAM-1 and EphB4 expression provided no evidence of a separate, venous capillary network expressing EphB4 in the CNS at this early stage (E9-E10). Rather, expression of a different EphrinB2 receptor, Eph B2, was seen in the neural tube as previously reported (Henkemeyer, et al., Oncogene 9:1001-1014 (1994)), where no gross morphological or patterning defects were detectable. In this case, therefore, the mutation does not appear to cause a non-autonomous phenotype in receptor-expressing cells, rather only an autonomous effect on ligand-expressing cells.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

3. (Amended) [The] A method [of Claim 1 wherein the artery-specific cell surface molecule is] for altering angiogenesis in a mammal, comprising administering to the mammal, in a therapeutically effective quantity, a drug which alters the specific binding of an Ephrin family ligand with [and the vein-specific cell surface molecule is] an Eph family receptor.

4. (Amended) The method of Claim 3 wherein angiogenesis is inhibited and the drug interferes with the specific binding [or interaction] of the [artery-specific] Ephrin family ligand with the [vein-specific] Eph family receptor.

5. (Twice Amended) [A] The method of Claim 3 wherein angiogenesis is enhanced and the drug enhances specific binding [interaction] of the [artery-specific] Ephrin family ligand with [its vein-specific] the Eph family receptor.

6. (Amended) The method of Claim 3 wherein the drug is an antagonist of the [artery-specific] Ephrin family ligand or an antagonist of the [vein-specific] Eph family receptor.

7. (Amended) The method of Claim 3 wherein the [artery-specific] Ephrin family ligand is EphrinB2 and the [vein-specific] Eph family receptor is EphB4.

10. (Amended) [The] A method [of Claim 8,] for selectively delivering a drug to arteries in a mammal, comprising administering to the mammal a complex comprising:

a) the drug; and

b) a component which binds [wherein the artery-specific cell surface molecule is] an Ephrin family ligand,

under conditions appropriate for the component of (b) to bind the Ephrin family ligand, whereby the drug is delivered to arteries.

11. (Amended) The method of Claim 10 wherein the drug is an anti-angiogenic drug and the component of (b) is an antibody specific for the [artery-specific] Ephrin family ligand[,] or a receptor of the [artery-specific] Ephrin family ligand.

12. (Amended) The method of Claim 10 wherein the [artery-specific] Ephrin family ligand is EphrinB2.

42. (Amended) [The] A method [of Claim 41 wherein the artery-specific cell surface protein is] for altering development of blood vessels in a mammal, comprising administering to the mammal a soluble polypeptide comprising the extracellular domain of an Ephrin family ligand or a soluble polypeptide comprising the extracellular domain of [and the vein-specific cell surface protein is] an Eph family receptor.

43. (Amended) The method of Claim 42 comprising administering to the mammal a soluble polypeptide comprising the extracellular domain of an Ephrin family ligand, wherein the Ephrin family ligand is EphrinB2 [and the Eph family receptor is EphB4].

72. (Amended) The method of Claim [71,] 10 wherein the drug is an angiogenic drug.

75. (Amended) The method of Claim [8,] 12 wherein the drug is angiogenic.